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The Globalization of the Pharmaceutical Industry

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THE GLOBALIZATION OF THE PHARMACEUTICAL INDUSTRY

A Major Qualifying Project Report:

submitted to the Faculty

of the

WORCESTER POLYTECHNIC INSTITUTE

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Abstract

Throughout recent history, the pharmaceutical industry has seen rapid modernization and globalization. The threat of disease, access to medicine for the poor, and rising health care costs have created a debate between generic drugs and their name brand counterparts. Looking at the historical evolution of the pharmaceutical industry allows for a better understanding of modern pharmaceutical issues. Generic and name brand drugs each have advantages and finding a compromise between patent protections and cheap generic drug production is the solution to modern global health issues.

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Chapter I: Introduction

Today the heart of the debate regarding the globalization of the modern pharmaceutical industry lies in the question of generic drugs versus intellectual property rights. The debate is of particular importance in the disease-ridden third world nations. On one hand, generics that are cheap and widely available could combat diseases more effectively than expensive name brands. At the same time, name brand prices drive the market through their ability to cover the high costs of research and development.

Generic drugs utilize the same active ingredients and dosages as equivalent name brand drugs but can be manufactured and sold for far less. Generics benefit third world countries and poor people in the West by making affordable drugs available for people of the world that are extremely poor and prone to large epidemics. At the same time, generic drugs undermine the property rights of the firms that do the research and ultimately test and invent these medicines. It is argued that the loss of these property rights weakens their ability to do the research necessary to invent life-saving drugs. With the widespread sale of cheap drugs, the large pharmaceutical companies thus lose money that is crucial to funding their research and development. The drug companies' argument is that without large corporate research and development, new drugs are not created and the generic drug companies have nothing to imitate once the 20 year patent is up, ultimately hurting the medical conditions in the third world. While convenient, cheap and easily made generic drugs are not widely available throughout the world. In 1995, the World Trade Organization adopted the TRIPS agreement (Trade Related Aspects of Intellectual Property Rights) creating a world-wide regulation of intellectual property such as prescription patents and pharmaceutical formulas. TRIPS was sought to maintain the profitability and economics of the pharmaceutical industry in the developed world. Prior to this agreement, there was little

regulation in the third world regarding generic drugs, allowing countries such as India, Brazil, and Thailand, to develop large amounts of generic drugs to sell to the developing nations at much lower prices than brand name drugs. For example, an AIDS cocktail developed in the West can cost between \$10,000 and \$15,000 per year, where in India, the identical cocktail ranges from around \$350 per year. TRIPS eliminated this ability as 20 year patent protection laws were set in place to satisfy the leading Western drug companies. Their argument is that the sale of generic drugs takes away their incentive to develop in two ways: First, the creativity of the pharmacists and researchers in major firms is compromised when a generic drug company imitates their drug formulas. Second, since the generic formulas of the leading drug companies' medicines can be available for up to thousands of dollars less per dose, name brand drug companies cannot make the sales they need to fund, while also hurting manufacturing.

The ultimate issues affecting the pharmaceutical industry deal with the argument of whether or not generic drugs will help the medical conditions of the world more than the patent protections of the current pharmaceutical industry. While patented Western drugs are sold at high costs in order to cover research and development budgets, third world nations suffer due to their lack of ability to afford drugs. These nations are the ones that need the drugs the most. It is estimated that only 5% of all research and development goes to the diseases that are the leading cost of death in Africa (Primbs). It is argued that if generic drugs could be manufactured and sold in Africa for cheap prices, then it would combat diseases more effectively. On the other hand it is argued that intellectual property rights for drug companies in developed nations would be compromised thus reducing R&D funding, hurting the economy of the medical industry, and inhibiting the creativity of western pharmacists and researchers. Major pharmaceutical companies also argue that this would hurt the developing nations in the long run as their

companies are the main research and development sources that develop new medicines. Proponents of preserving the IP rights of drug companies also argue that the influx of cheap generic drugs from nations such as India or Brazil would exceed the ability to regulate the quality of these drugs. The U.S. and other Western nations argue that generic drugs would create a global pharmaceutical market that would allow potentially harmful generic drug formulas to enter developed nations and damage the health issues in developing nations in two ways: The first way would be by not providing effective medicines to fight existing diseases, and second, by harming the population with faulty medicinal compounds that are potentially deadly. To understand how this problem has arisen, one must look at the development of the pharmaceutical industry over several centuries and different scientific and cultural practices that came together to form the industry.

Prior to the 19th century, the pharmaceutical industry was confined to small scale apothecaries, simple laboratories in the back of local shops, and in the hands of self-proclaimed druggists. Medicinal shops date back to Greek and Roman times, with a more advanced drug industry found in the 6th and 7th centuries in the Middle East, before expanding into Europe. By the 18th century, countries such as Britain, Germany, Switzerland, and even the American Colonies had taken a keen interest in this small scale industry because of the growing interest in therapeutic remedies, as well as advances in the field of chemistry that had medicinal implications. Around this time, the colonization of North and South America led to the discovery of various indigenous plants, beginning what pharmaceutical historians call the “Age of Botanicals.” Many of these plants were developed into medicinal remedies by the natives to those lands. When Western colonists encountered these native remedies, it sparked a study of indigenous plants allowing for the discovery and testing of many more indigenous remedies that

could be utilized by colonized peoples as well as Europeans (Tsinopoulos 2). Along with the Industrial Revolution, a large growth in the biological sciences and the growth of state-sponsored universal education, the pharmaceutical industry grew exponentially. With the ability to discover, study, and test new medicines, as well as the technological ease of manufacturing came the consolidation of all aspects of this process into large pharmaceutical companies. Scientists, pharmacists, manufacturers, researchers and everything in between now worked under one name for the common goal of high levels of production and innovation. With this production came the need to protect new medical formulas via patents and intellectual property rights. Patent laws motivated companies' creativity and innovation and many gains were made in terms of disease fighting capabilities. In order to truly understand the complexity of this evolution, a closer look must be taken at the historical background of all of the various historical processes that evolved into the modern drug industry. After examining the history of the modern drug industry, this study will conclude by returning to the analysis of the debate about intellectual property rights and the need for cheaper generic drugs in the developing world.

Chapter II: The Early History of Pharmaceuticals

The historical roots of modern pharmacy lie within two fields of pseudoscience that date back to ancient civilization. To fully understand the evolution of modern the pharmaceutical industry, one must begin with the study of alchemists and apothecaries. These spiritualists, scientists, and healers sought everything from the transmutation of metals into riches, to the power of immortal life. As the science and technology grew, so too did the field of medicine, taking forms of early science from Asia all the way to Europe and molding them into something beneficial for the well being of society.

One of the earliest traditions to impact the modern pharmaceutical industry is that of alchemy. Alchemy is a combination of primitive inorganic chemistry mixed with philosophy and a search for immortality and ultimate wisdom. Beginning in Egypt, various forms of alchemy spanned three continents between 5000 B.C.E., continuing to be practice in one form or another until the middle of the 17th century in Europe when it transformed into modern chemistry.

In the West, early practices of alchemy were performed by the Greeks and Egyptians. Their alchemical methods were central to their search for eternal life and philosophical wisdom, as well as their religious practices. The Egyptian King, Hermes Trismegistus was considered a founder of alchemy. Around 1900 B.C.E. he was the first to compile the works of Egyptian spiritualists dating back to the dawn of civilization. His ultimate desire was to unlock the knowledge required to understand the operation of nature (Cockren). Much like the work of the Egyptians, these ancient societies were able to make many scientific discoveries that were unimaginable even in the centuries to come, however much of their work was destroyed around 290 C.E. by the Roman Emperor Diocletian. Diocletian ordered that all alchemy texts be

destroyed in order to prevent Egypt from amassing riches through transmutation that could facilitate a successful revolt within the empire. One important book survived, known as the Emerald Tablet which became the main book of alchemy. The contents of this text deal with the transmutation of various metals into gold, as well as herbal compounding and other theories on the original elements. Egyptian and Greek alchemists had theorized that earth, wind, fire, and water, were the four elements that comprised and created everything in nature. While we now know this is far from scientific, the traditional classification of elements had become a stepping stone into modern chemistry that had a large impact on the pharmaceutical industry in return.

At the same time as the discovery of the Emerald Tablet, the Chinese were practicing their own unique form of alchemy. Taoist spiritualists were seeking to study and take part in deep meditation. Alchemy arose as they sought to remain pure both mentally and physically. *Wai-tan*, or external alchemy, was the use of drugs and herbal compounds in the search for immortality, while *nei-tan* was known as internal alchemy and centered around yogic meditation and internal reform of the spirit. The earliest known written reference to Chinese alchemy came when Christianity reached the far-east. The Chinese were seeking the “Elixir of Life,” which was believed to be able to grant anyone eternal life. Along with their quest to find this elixir, they proposed that various, less potent compounds could cure illness and heal the body. These elixirs would allow pure meditation and ultimately become an early pharmaceutical system (Cockren).

The Egyptian alchemists sought to transmute metals into gold, and to harness the science behind nature’s doings for the purposes of power and religion. The Greeks and Romans were looking to record and understand the make-up of nature for the sake of philosophy and science. The Chinese were attempting to find immortal life and in doing so became keenly interested in

the development of effective medicinal elixirs. With the emergence of the Silk Road, and various East-West trade routes between Europe and Asia, the Middle East became the place where the various styles of alchemy met. Arab alchemists were the first to discover corrosive compounds, oxidation, while also studying the effects of mercury and nitrates. They claimed to be able to transmute metal into gold, much like their European counterparts, while also beginning to explore medical compounds as the Chinese did. This multi-dimensional practice of alchemy was spread west and east via trade routes and became the basis for the methods practiced in Medieval Europe.

With the fall of Rome, much of the early work of alchemists was lost for Europe allowing the Arab form of alchemy to take root in European science. With the arrival of the Moors in Spain, came their alchemical knowledge as well as Islam. Arab alchemists are credited with the first practice of modern scientific method, as they were the first to bring structure to the study of nature's chemical makeup. In the eighth century C.E., the scientist Jabir Ibn Hayyan took the classic elements and expanded the system into a table of 7 elements and chemical processes, becoming the father of the medieval periodic table. Islamic alchemists and medical scientists created many tools that still exist today including the first distillation apparatus. The 12th century also brought the first Arab medical schools and some of the first pharmaceutical scientists emerged based around alchemy and a motivation to create and test medicinal elixirs. Through conflict with the Holy Roman Empire, alchemy soon spread across Europe and became one of the pseudo-sciences in medieval times (Holmyard).

During the middle ages, alchemy was associated with wizards and loners often believed to be in contact with the devil. Their motivation was to defeat disease, prolong life, and control the elements. While they were rarely accepted by the majority of society, there were a number

of scientific breakthroughs that occurred in these alchemist workshops. The evolution of empirical scientific thought began to replace abstract speculation. The motivating factors of prolonging and improving life are what still drive doctors, pharmacists and scientists today. Medieval alchemy became known as “hermetic science” because of its connection to the surviving work of the Egyptians, The Emerald Tablet. Many works emerged on how to prolong human life, find immortality, and create compounds to improve one’s health.

The Inquisition took the lives of many of Europe’s alchemists, while burning thousands of books and papers regarded dark magic and works of the Devil. At the same time, rich merchants were entrusting their riches to alchemists in order to experiment with Egyptian transmutation theories with hopes of multiplying their fortunes. This trend resulted in a corrupt group of “alchemists” that claimed to be able to transmute metals into gold, that would steal the money and metals from the merchants. As this trend became more popular the true scientists became discredited and this primitive scientific field lost much of its momentum. (Cockren).

In the 13th century, one theory was asserted that would survive to transform the field of alchemy into chemistry in later centuries. In the middle of the 13th century, Albertus Magnus, a philosopher and scientist, claimed to have discovered what he believed was the “Philosopher’s Stone.” This was a tool which was said to be able to transmute substances into gold. He passed his work on to his pupil, Thomas Aquinas who continued to write about the stone. While the stone was not real, it sparked thought regarding the elements. In the 1500s, it was widely believed that the four elements--earth, wind, water, and fire--were various forms of one element. The medieval theory of the elements evolved from the belief that the Philosopher’s Stone could change substances into other substances resulting in three major theories of modern chemistry. These theories were that matter is not created or destroyed, the theories behind the periodic table

of the elements, and the theory of compounding basic elements into more complex chemical bodies. Compounding elements and substances would of course become vital to the chemical industry's ties to the pharmaceutical industry. Alchemists were still limited as they were often highly spiritual, monetarily motivated, and seeking power or scientific enlightenment. The need for a more specialized industry had arisen from the development of medical compounds through alchemy. The stage had been set for the apothecary. (The Alchemy web site on Levity.com).

Apothecaries

Similar to the alchemists, apothecaries studied medicinal formulas, therapeutic compounds, and even practiced surgery and diagnosed diseases. Apothecary shops can be traced back to Baghdad around 700 C.E. and saw much popularity in the Middle East during the middle Ages. Arab apothecaries focused primarily on medical compounds and the sale of herbs and spices. Their shops were laboratories as well as dispensaries.

The apothecary shop that evolved into today's modern pharmacy however, took its roots in Europe around the 13th century. The title of apothecary is derived from the word "apotheca," which described a place where spices and herbs were stored (The Worshipful Society of Apothecaries of London). Credit for some of the most advanced drug research and medical work can be given to Germany and Switzerland. At the same time, London is heralded as the center for the evolution of the modern pharmacy. Beginning in the middle ages, London's trade guilds were dominated by the Livery Companies. The Livery Companies were responsible for the regulation of wages and labor for a specific profession. The pharmaceutical industry in London began with the Guild of Pepperers, which was formed in 1180. The Guild was responsible for the regulation and documentation for the accurate weighing and compounding of spices, as well

as the sale of these items (Thompson). In 1373, the Guild became a Livery Company known as the Worshipful Company of Grocers. Originally, the Grocers were primarily involved in the trade of spicery, becoming intertwined with the field of medieval medicine as a result. Spicer-apothecary shops began to emerge across Europe with particular prominence in London. The College of Physicians was the ultimate authority on diagnosis and medicine; however physicians were expensive and scarce in comparison to the apothecary. The spicer-apothecaries became well respected as a result and the neighborhood apothecary shop was the common authority on all things medical for the local population. The respect gained by apothecaries created two major issues that hindered their ability to achieve independence as a unique trade (The Worshipful Society of Apothecaries of London).

The grocers sought to keep spicer-apothecaries together because of the success they brought to the trade of spices and the Company of Grocers. In London, along with similar instances in France and Germany, petitions were made by apothecaries between late 1500s and early 1600s. These petitions sought independence for the apothecary. They believed their skills were specialized to the point where they needed to unify and practice as a unique field of medicine. They had been actively formulating and documenting their medicinal work for several hundred years, and were essential to the general public. Once again, the next evolutionary step took place in London. Gideon de Laune, the apothecary to King James' wife, The Anne of Denmark, began a separatist movement for apothecaries. With the backing of the Royal family, a charter was granted in 1607, and the Worshipful Society of Apothecaries was founded (Thompson).

At the same time, physicians were seeking to eliminate apothecaries. They felt that their work was being undercut by the apothecary. The apothecary was able to identify drugs, create

therapeutic compounds, measure and sell medicines, and operate laboratory equipment. In the eyes of the physician they were nothing more than that. On the other hand, given the shortage of physicians, and the nature of the apothecary's work in general, they were often found diagnosing illnesses and practicing medicine. In France, beginning in 1513, physicians began issuing do-it-yourself handbooks on how to concoct medical and herbal remedies as well as diagnose symptoms. The main book that they used to denounce apothecaries was the *Le Medicin Charitable*. London followed suit by creating dispensaries where drugs could be obtained by the poor in small doses for even lower prices. Still, apothecaries survived long enough to see the creation of the Worshipful Society of Apothecaries and never looked back.

In the case of William Rose in 1703, the House of Lords proclaimed that it would be hurting the general public to prohibit the prescription of medicines by apothecaries. After this point, apothecaries began describing themselves as chemists and druggists and were able to practice medicine to some extent. They also perfected the apothecaries' system, a system of units used to measure and compound medicine. In 1815, the last evolutionary step transformed the apothecary of the middle ages, into the modern pharmacist. The Apothecaries Act of 1815 established medical qualifications for the apothecary, requiring schooling in botany, anatomy, physic, and various other medical texts. On top of those classes, six months in the field at a hospital was also required (Porter). With a new educational requirement and independence from physicians, this newly regulated field became a well respected medical institution. While family run apothecary shops with well respected names and no medical degree from the Society of Apothecaries still existed, this regulation was the beginning of the end for any apothecary with no formal education (Porter).

With more money coming from success, advances in equipment and research for the apothecary were made possible. The Society had established the Chelsea Physic Garden in 1673, which became the largest collection of medicinal plants in Europe, with over four acres. The Chelsea Physic Garden established a seed exchange program and is partly credited with much of the growth of cotton in colonial Georgia. With the growth of the modern pharmaceutical industry after the Apothecaries' Act of 1815, the garden provided a place of research and was extremely beneficial to the field of medicine (Minter).

Around the mid 1800s, all of the leading pharmaceutical nations began offering courses of study, and licenses to practice the sale of pharmaceuticals and a member of the field could obtain a license in order to gain a more reputable standing in the medical field (Russell, 135). At the same time, the scientific field in Europe and the United States had made medical advances in the area of disease identification and breakdown. Diseases could now be identified by specific symptoms and were increasingly cured as a result. Sciences like chemistry and biology were poised to join with the modernized pharmaceutical industry to turn into large scale commercial pharmacies as the modern era began at the turn of the 20th century.

In terms of regulation, education, and technology, the pharmaceutical industry had grown a great deal, however one thing remained. It was going to take another complex variable to turn this young science into a modern industry. With the discovery of the Americas came a wealth of natural resources, such as seemingly endless lands, and even native knowledge. With the ability to research, test, and synthesize indigenous remedies already in existence, the field of medical research would grow exponentially at an unprecedented rate. The true beginnings of the

globalization of the pharmaceutical industry, and the positives and negatives of European colonization of undeveloped regions of the world also led to the debate over generic or brand name drugs.

Chapter III: Age of Exploration and Scientific Revolution

In the Early Modern Era, scientific advances were not the only advances seen. The quest for knowledge, thirst for exploration, and desire for resources through trade, brought the world together like never before. Soon, the discovery of the Americas would shape the pharmaceutical industry by providing an source of resources and a motivation for research that fueled the pharmaceutical industry's growth.

Modern pharmaceutical practices grew in large measure out of a number of factors. Few factors impacted the development of the pharmaceutical industry more than colonialism. The development of the New World, the trade of Western botanicals, and the general impact of the industrial revolution on science and technology were essential factors in making pharmacy a dominant global industry.

Between the 1400s and 1800s, much advancement in the pharmaceutical industry came from the discovery of the uses of various indigenous drugs by Europeans and Colonists. Motivating the search for new indigenous drugs was the desire of the French, English, Dutch, and Portuguese to exploit the trade routes used by the Venetians and the Turks in the Orient. These nations wished to trade for Oriental spices and botanicals while also expanding the pharmaceutical industry on a global level. The effective relationship between the apothecary and the spicer came from this trade because most of the pharmaceuticals at this time were compounds of spices and herbs. With the Age of Exploration, global exploitation of indigenous botanicals played one of the largest roles in the formation of a true industry for medicine (Kremers).

The discovery of North and South America, and the lessons learned about indigenous medicines from the Oriental spice trade, began a massive search for useful flora in the Americas.

Beginning in South America and spreading all the way to Canada, explorers were finding uses for many indigenous botanicals from the New World. Two major factors played a role in the expansion of the drug industry after the discovery of the Americas. The first factor was the uses of various plants and medicinal compounds by indigenous people. In Central America, the Spanish found a Mayan culture that had over 400 documented medicinal uses for botanical drugs. Adopted by the Aztecs from whom the Europeans gained this knowledge, the translated list became known as the Badianus Manuscript, and was given to the Vatican in 1552, resulting in widespread publication across Europe (Kremers).

At the same time, the explorers of North America were recording their encounters with the native medicines and therapeutics. Nearly 200 botanical drugs were documented in America and Canada between the discovery of North America and the American Revolution, while roughly 50 more uses came from Mexico and the West Indies. As a result, the exploitation of American botanicals had begun, and more emphasis was put on the Atlantic trade routes by the European scientists and merchants. The new emphasis eventually resulted in less focus on the widespread use of natural resources by Europeans, as more focus was being placed on permanent settlement by this time.

While the documented use of botanicals by American natives was a stepping stone towards a modern pharmaceutical industry, the colonization of the west led to some of the greatest advances in medicine. The Jesuits are credited with the single most important medicinal discovery from the New World. The discovery of the uses of Cinchona, or Peruvian bark, to treat malaria became the benchmark example of colonialisms impact on the advancement of the medical industry. Cinchona (source of Quinine), was one herbal remedy that originated in South America around the mid-1600s. Jesuits, colonists, new world apothecaries with European

training, and explorers had documented their observations of native people's uses of New World, African, Indian, and Pacific drugs, but never before had a European group identified, tested, and exploited such a successful and necessary drug on their own in the New World (Kremers).

In the early 18th century, a concerted effort was made by James Oglethorpe to transplant indigenous remedies and useful herbs from the Spanish colonies in South America, Central America, and the Caribbean. Because Oglethorpe's colony of Georgia had already supported the Worshipful Society of Apothecaries' push to grow cotton in his colony, he gained their financial and scientific support in his new endeavor. British scientists and botanists traveled the Spanish lands searching for ipecac, cinchona, cochineal, saparilla, balsam, and various additional medicinal herbs. A botanical garden was established in Savannah; however it ceased to be utilized as a result of Spanish opposition, until the end of the Revolutionary War (Kremers), however, the effects of the transplantation of botanicals to artificial gardens in Georgia and the colonies had already been established. For the first time, plants were brought to Georgia to be studied and grown. At the same time, the scientist John Ellis began writing directions on how to transfer seeds across the Atlantic, as well as a catalogue of foreign plants in order to promote medicinal use and greater agricultural success.

Around the time of the American Revolution, the Americans compiled all of the indigenous drug uses into the *National Formulary* and the *United States Pharmacopoeia*, resulting in growth in the pharmaceutical industry in the early 1800s. Native drugs came to the forefront as scientists began studying the effects of drugs on various symptoms that had been associated with certain diseases. The 19th century pharmaceutical industry was a result of the discovery and use of non-European remedies like digitalis, cocaine, aspirin, and quinine. These discoveries resulted in a trade industry in the area of medically beneficial drugs from the colonial

world (Tsinopoulos 2). By this time, Europe had wide access to American botanicals, which they studied and compounded while America was creating its own apothecaries and dispensary shops, and studying the medicinal uses of these indigenous drugs as well. With the cross pollination of American and European science and materials came a boom in the pharmaceutical industry. Scientific advances in biology around the same time resulted in the knowledge of what to study and how to identify and treat diseases, coupling perfectly with the boom in knowledge about locating, utilizing indigenous botanicals in the America and Europe.

The Pharmaceutical Industry's Ties to the Field of Biology

In the 1800s, the field of biology established the relationship between the medical value of natural substances and the newly accepted “germ theory” (Tsinopoulos 2). This theory was also known as the “pathogenic theory of medicine” and dealt with the idea that microorganisms were the cause of most diseases. The problem with germ theory was the idea that disease was spontaneously generated. This idea dated back to the 2nd millennium B.C.E. with the writing of the Atharvaveda, or the fourth book of Hinduism. The Atharvaveda widely expanded upon in the 10th century C.E. is the earliest dated book of medicine to propose the idea that disease was created spontaneously.

The first to challenge the idea of spontaneous generation was Girolamo Fracastoro (1478-1553), in 1546. He believed that disease could be spread over short or long distances, through contact or no contact, by tiny seed-like objects. However, it was not until the late 1600s that the first concrete challenge to this ancient theory could be made. Anton Van Leeuwenhoek (1632-1723) was a glass grinder and a lens maker in the Netherlands. He created the first lens that was able to observe a living microorganism. This discovery sparked a wave of scientific research

that led up to the beginnings of the germ theory (Black 8). From here, scientific statisticians like John Snow in England, were able to begin to track where diseases were coming from. When a neighborhood was able to be isolated as the birthplace of an outbreak, further studies were able to be done regarding causes, symptoms, and cures for the specific illness. Scientists such as Louis Pasteur were able to conduct experiments that proved that disease-causing microorganisms lived in the air, but were not created by the air, and could contaminate water, living organisms, and so on, through exposure. This was the initial formation of the germ theory. Disputed at this time, Robert Koch was able to create a series of steps known as the Koch Postulates that were able to identify a specific microbe and the disease it was responsible for. The Koch Postulates were narrowed down to 4 sets of criteria that a microbe must meet to be known as a disease causing agent, and identify which disease it is associated with. They were finalized in 1890, and are still the basic theory behind modern disease identification.

With the Koch Postulates, and the acceptance of the modern germ theory, came an increased interdependence between the biological, pharmaceutical and chemical industries. The first impact of biology on the pharmaceutical industry was the discovery and use of chemotherapeutic agents in the early 1900s. Chemotherapeutic agents were the first broad name for synthetic drugs and antibiotics, or substances produced by one microorganism that inhibit the growth of another. Experiments were done to identify agents that were harmful to a disease causing microorganism. If the harm to the microorganism far exceeded the harm that the agent inflicted on the host, the agent became the subject of a new synthetic drug or antibiotic.

With emergence of the use of indigenous remedies, the acceptance of modern germ theory of medicine, and the ability to isolate diseases through biological means, the combination of the biological and chemical industries greatly increased the success of the modern

pharmaceutical industry. The biological theories behind the isolation of diseases as well as agents to counter them resulted in early antibiotics. Now the modern pharmaceutical industry would require combination with the chemical industry to allow for mass production, as well as increasingly potent synthetic drugs that resulted from chemical combinations based on biological theories. As a result, large pharmaceutical divisions emerged within existing chemical and biological firms in Britain, Germany, and the United States, among others.

The Impact of the Chemical Industry

Parallel to the biology industry in the mid to late 1800s, the chemical industry increasingly became a factor in the emergence of the modern pharmaceutical industry. The title of “chemist” saw sporadic use beginning in 1783 with Antoine Lavoisier’s Mass Conservation theory. Between 1783 and 1900, “chemist” slowly overtook “alchemist” as the preferred title. Chemists began joining these pharmaceutical divisions in order to test the medical benefits of the combination of various chemicals. Coupled with the Industrial Revolution, the mass production of successful medicinal compounds became the basis for the modern pharmaceutical industry. The greatest example attributed to the formation of the pharmaceutical industry as we know it, dealt with Diabetes. Diabetes had been a deadly disease that had been seen in great numbers throughout history. At the end of the 19th century, scientists had been able to isolate the pancreas as the culprit for this disease. They had discovered that a certain hormone was the cause for the lack of insulin that spelled almost certain death for all with diabetes. In 1921, a Canadian physician named Sir Frederic Banting was able to isolate this hormone. Banting was able to synthesize a drug that could boost insulin levels and stabilize diabetes. Banting’s studies, as well as similar advances resulted in the modern pharmaceutical industry taking its root. A US-based

company gained the rights to manufacture the drug under property right laws at the time. Technological barriers were overcome in order to mass produce the drug, and the importation of raw materials, extraction of necessary compounds, and synthesis and purification of the final product were all perfected. The chemical, biological, legal, and industrial fields had all combined on a large and effective scale to make up the modern pharmaceutical industry. Shortly after these advances, the discovery of Penicillin was made in 1928. The stage had been set for the discovery and development of many key advances in the global pharmaceutical industry (Tsinopoulos 2-3).

Chapter IV: Consolidation and Globalization in the Modern Era

While the impact of colonialism brought countless monetary and scientific rewards to the pharmaceutical industry, some legal debates began for the first time. The modern issue of third world exploitation and generic or cheap, identical versions of name brand drugs saw its beginnings in the American Colonies. For the first time, a newly discovered areas of land, with undeveloped infrastructure and a less militarily and scientifically advanced indigenous people became a subject of exploitation. Fortunes were made, and native civilizations were knocked down. The indigenous drugs from America and the pharmaceutical industry as a whole, however, benefited from the positives of advances in medicine and trade creating large scale growth in the industry. At this time, there was virtually no regulation on trade, patents, and monopolies in the medical field leading up to the 1900s. These issues that the world began to see during the emerging development of the Western Hemisphere would come back into play in the future with the modern arguments involving the development of generic drugs. As the scientific fields of chemistry and biology grew, they were quickly weaving themselves into a set of modern sciences that the pharmaceutical industry depended on. As the industrial revolution evolved, and technology grew, the pharmaceutical industry was becoming a self-sufficient machine such as we know today.

A wealth of natural resources, emerging nations, advancing trade systems, and a rapidly advancing scientific field were allowing the pharmaceutical industry to evolve at a large rate. Educational requirements were found across Europe and America, and pharmacists were finding independence from physicians for their field of medicine. Local pharmacies were showing up everywhere, with the ability to mix and compound their own drugs and to prescribe and sell goods to their local areas. At the same time, advances in science and technology with particular

emphasis on mass production were on the rise. Important discoveries with antibiotics, and two world wars would show the world the effectiveness of a pharmaceutical company that could supply their own raw materials, technology, scientists, medical experts, and everything in between. With the emergence of these companies came legal issues and ethical questions that would both plague and help flourish the modern pharmaceutical industry through the 20th century.

In the late 1800s, the biology industry had made a number of advances in disease identification and diagnosis became far more accurate. Germ theory taught us to search for causes and utilize symptoms to decide how to treat specific ailments. At the turn of the 1900s and into the 1920s, the chemical industry expanded upon these theories and practices to treat diseases by synthesizing drugs based on need, but the pharmacy was still a far cry from the pharmacy that sells a remedy for virtually everything that we know today.

In the early 1900s, the majority of prescriptions were filled by local pharmacists. Pharmacists at this time were apothecaries with increased knowledge and resources, acting in the same traditional manner. They would mix powders and creams, and coat their own pills, attempting to create decent tasting and non-poisonous medicines to treat various diseases. While they were educated in medicine, and utilized documented ingredients, dosages and compounds were still a fairly inaccurate and inconsistent science.

With the arrival of the 1920s and the discovery of Banting's insulin boosting medicine to combat diabetes saw a push for an industrialized industry. There was enough biological and chemical knowledge regarding medicine to mass produce drugs in order to serve the population more effectively. Pharmacists could now purchase ready-made compounds from wholesale distributors for their local pharmacies. Companies began marketing drugs under brand names by

gaining primitive medical patents and property rights for their products. Pharmaceutical companies such as these began drawing from the local druggist population to create a workforce made up of chemists, biologists, industrialists, and the local pharmacist that everyone was used to calling “Doc.”

On the other hand, many remained in their local drug stores, however their jobs were changing with the involvement of chemists and creation of large pharmaceutical companies. Pharmacists were now responsible for far less knowledge, only needing to know which product treats which disease, and occasionally the reasoning behind the pharmaceutical cure. In 1932, it was required that all pharmacists in the United States hold a Bachelor’s degree. Many European nations followed suit shortly after. The difference between this new degree and the prior certification was that pharmacists were now studying a heavy dose of chemistry along with a broad range of the other physical sciences. There was less emphasis on compounding and the specifics of botany and disease identification due to the industrialization and consolidation of the pharmaceutical industry.

Local pharmacists began selling products like foods, medical supplies, and other assorted items to maintain a source of income. Between the 1920s-40s, the local pharmacy was evolving into a medically oriented convenience store where prescriptions could be filled. At the same time the “apothecary” of old was falling victim to the consolidation of pharmacy and the sciences into companies that could pool from all industries to be self subsistent (Holcomb).

With advances over the previous two decades, and the effects of World War II in terms of casualties and need for medicine, the 1940s became known for advances in antibiotics. Large numbers of infected soldiers resulted in the need to discover antibiotics and develop advanced penicillin-based compounds. Penicillin, discovered in 1928, is regarded as one of the greatest

medical discoveries in the modern era, leading to the development of many antibiotics and disease and infection cures as a result. Scientists were now able to develop compounds that could cure specific diseases. Antibiotics were being prescribed by doctors at a large rate. Pharmaceutical companies were receiving a large amount of monetary aid in order to research and mass produce antibiotics to treat the wounded soldiers. Two European discoveries from the 1930s joined penicillin in the WWII mass production boom. They were Sulfonamide, which was used for pneumonia and resulted in many sulfur based antibiotic compounds, and Prontosil which was able to control bacterial infections at a high rate. Sulfa was issued to each soldier during WWII and was often the first item put onto an open wound, resulting in far more effective treatment and greatly increasing the survival rate. Pfizer, an early pharmaceutical company, was able to perfect a process to mass produce penicillin at a safe and effective rate. As a result of the casualties of war, the United States government authorized and funded 19 companies to use Pfizer's process to mass produce antibiotics. Once again, European nations followed suit (Steinert, 2000).

Other medical compounds such as the aforementioned sulfa and plasma (a protein-salt liquid that accounted for a large portion of blood content) were mass produced and government funded as well. With cures such as these, came many patients that were kept alive but still in pain. A market for large scale production of pain and fever reducers was created as a result. Squibb created a way for an opium based morphine compound to be administered on the frontline by medics. This was called a *syrette*, and was similar to the modern syringe (Steinert, 2000).

The Pacific theater in particular saw a need to fight malaria. Quinine based drugs were also mass produced from existing formulas to save the lives of many soldiers in the East.

Lessons learned and advances made during WWII would change the industry for good. The apothecary as it had been for the previous decades faced extinction, and the mass production of safe and effective drugs was seen on a large scale (Steinert, 2000). With the end of the 1940s, the post war society saw a need to regulate the hasty dosages issued during the war. The FDA, for the first time in history, regulated mass produced drugs in 1951. Over-the-counter, and prescription strength drugs had been divided for the first time, creating a broader market for the latter half of the 20th century. (See Todar's Online Textbook of Bacteriology).

The Post-War Boom

Perhaps the largest growth in the pharmaceutical industry came in the 1950s due to two major factors. Scientific understanding of human biology reached new levels. Genetics and DNA research led to an unprecedented understanding of the body as well as diseases. At the same time, the growth in the antibiotic industry had achieved great success. This growth resulted in a great deal of good as it solidified the need for an ever-growing pharmaceutical industry. The majority of this growth can be attributed to the lessons learned from WWII. Roughly 500 new types of medicine entered the market during the 1950s alone, opening up new dimensions in the growth of the pharmaceutical industry. These new dimensions were marketing as well as regulation. Television advertising and giant billboards showcased the ever growing industry to the majority of the population. As a result, more money was raised, drugs continued to be developed, and faith and effort in the industry soared. At the same time, the governments of the United States, and the leading European nations saw the need for regulation. In America, the FDA issued new regulations regarding testing and certification, while also making the prescription of drugs a widely regulated endeavor (Gale Encyclopedia).

While diseases and bacteria had been relatively stable since the outset of the industry in the early 1800s, the 1950s saw a spike in bacterial evolution. Bacterial resistance to antibiotics was noticed, forcing the pharmaceutical industry to push for higher levels of research and development and a larger production rate (Todar's Online Textbook of Bacteriology). With higher levels of research came methods such as animal testing as well as the watchful eye of the FDA. In the 1960s, a drug developed in the WWII era to fight the effects of nerve agents called thalidomide came back to the forefront. Animal testing and other research showed that this agent could settle the stomach and aid sleep in pregnant woman. Over a span of four years, it was sold under nearly 50 names in roughly 100 countries to pregnant women looking for relief of morning sickness. By 1962, nearly 10,000 children were born with severe birth defects as a result of the medicine. Animal testing had misled scientists to belief this drug was safe to be taken by pregnant human women. Because of this tragedy, the FDA began its longstanding policy of leaning towards what opponents believe to be over-regulation (Primbs, 1998). On one hand, strict regulation and intensive research and testing were viewed as preventative measures to eliminate such tragedies as the thalidomide incident. On the other hand, opponents claim that this regulation leads to more death as a result of the denial of life saving medication to those in need. They believe that the over-regulation of the pharmaceutical industry will have a greater negative impact on health conditions than the chance of a medical tragedy that occurs almost never. Another argument made by the FDA is that they need to be there to ensure that the proper testing is done and information is provided so that companies do not just hastily manufacture drugs to make money. Opponents to this view say that there is no reason for a drug company to perform any less testing than necessary, or withhold any information from consumers and

physicians alike. Poorly working medicines only hurt the bottom line of sales, and another tragedy would virtually eliminate a pharmaceutical firm's existence (Primbs, 1998).

Aside from the growing debate between the FDA and the Pharmaceutical Industry, the decades leading up to the end of the 20th century were marked by vast advances in scientific theories regarding DNA, technological advances that could have never before been imagined, and the study of the causes of diseases. For the first time, many of these theories were widely accepted, allowing for research expansion and greater funding. Cancer research had begun to advance, and the biotechnological field was born. Biotechnology refers to techniques in biological research that seek to perform such tasks as tissue-culture or gene transfers, and so on. Biotechnology combines genetics, cell biology, and various other fields to artificially manipulate or alter some type of organism. For the pharmaceutical industry, this also meant a better understanding of test subjects and medicinal effects on various parts of the body. Now, specific medicines could be created based on how they affect certain genes or the proteins of certain organs, based on a specific disease.

Arguably the most significant disease to impact the globalization of the pharmaceutical industry was AIDS; discovered in the 1980s, AIDS is to date, an incurable disease that plagued the entire globe, with particular destruction in Africa. Africa, a developing continent, has had little access to medicine of any type. With a growing epidemic and the emergences of biotechnology in recent years prior came three major events. First, genetically manipulated organisms became subjected to patent laws. This was particularly important to small biotechnological firms in the 1980s as it was one of their main focuses. Second, the Bayh-Dole Act allowed for patents to be granted to recipients of federal research funding. This allowed for an influx of money to small and large companies alike, giving them more incentive as well as

ability to research and develop. Finally, Genentech became the first biotech company to go public. Over the next decade thousands of small biotechnology firms emerged and grew, creating jobs, competition, and most importantly-medicines to fight cancer and AIDS. The trend that is still occurring today of massive mergers began as well. Small companies were banding together or being absorbed by larger firms to create large pharmaceutical companies of sizes never before seen (Bowden).

The Modern Pharmaceutical Industry

The new millennium marked the start of a great debate regarding the pharmaceutical industry over the past two decades. Countries like the United States, Germany, and Britain had made large advances in this field as a result of mergers, regulations, and scientific breakthroughs. Plans like that of America's Health Management Organizations (HMO) also emerged during the 1980s to contain the rising costs of medicine. Intellectual property laws emerged to also protect the rights of pharmaceutical companies worldwide. 20 year patents were enforced by the World Trade Organization's TRIPS agreement in the 1990s. In countries like America, prescription drugs are largely regulated by the government and pharmaceutical companies are given a virtual monopoly by the restriction of the importation of global pharmaceutical products. According to the drug industry, companies must charge prices beyond their costs of production in order to cover their large research and development budgets. Arguments for international regulation say that *generics*, or drugs manufactured with the same active ingredient as the name brand, as well as drugs made in leading pharmaceutical nations such as India, may not be properly tested or safe for the U.S. population. On the other hand, the medical industry will still argue that health is jeopardized when medicine is unaffordable to many citizens (Paul).

While that is just one small example of the global debate within the pharmaceutical industry, the major issue is the role that should be played by the free market. A free market would lower trade barriers allowing market price to dictate what citizens pay, while patent laws would still exist. With most of the drugs coming from the Western world, availability would become more open to 3rd world nations that were in dire need of cheaper drugs. Along with the issue of free market competition for drugs, comes the debate on whether generic drugs do not do damage to the research and development initiatives of pharmaceutical companies. One example of the ability of a generic drug became evident in 2001 as an AIDS cocktail developed in India could be imported by developing nations at a rate of \$350-600 per year. The exact same cocktail costs between \$10,000-15,000 when manufactured in the United States. The Indian firm, Cipla, challenged that the pharmaceutical industries ability to decide which company manufactures what drug, and the World Trade Organization's patent laws restricting the production and sale of generics is severely hindering the potential health benefits for third world nations. In 2003, the WTO amended its patent laws in order to allow African nations to import low costs generics due to their inability to manufacture necessary medicines at home. This proved to be successful in many ways by allowing drugs to become available for lower prices at distances closer to the drug patients. This was however, only developed on a small scale. The ultimate challenge that the modern industry is facing deals with the fact that developing nations record the largest number of diseases, yet the drugs necessary to combat and control these diseases are hardly affordable in the United States, let alone the third world. At the same time, diseases that are highly curable in developed nations, are often deadly in the 3rd world. Much of this is attributed to regulation and the lack of availability of cheap, patented, western medicines (Holland 1-3).

On the other hand, a market allowing any sort of generics can allow for the international stealing of patented formulas. Unregulated generic drug development can also lead to potentially harmful products furthering the health problems of the third world. Generics manufactured in places like India and Brazil are subject to less regulation, less sanitary conditions, and are more susceptible to formulation issues that can lead to incorrect dosages and even death. Finally, the unregulated availability of generic drugs can put the industry leaders of pharmaceutical development in a financial bind due to the unfair competition by companies that violate their patents. Inventors, developers, and generic drug critics will argue that the sale of cheap drugs will ultimately inhibit their ability to produce effective medicinal formulas by taking away the necessary funding for research and development. While the leading pharmaceutical firms have much of their funding tied up in research and development, the generic drug companies are able to focus all of their money on manufacturing alone and can sell their products for prices that the leading companies cannot compete with. That is why the major pharmaceutical firms argue that there is a need for patents and that their high prices are the only thing truly driving the success of the industry. (Gentleman, NY Times, 2007)

Chapter V: Conclusion and Recommendations

With an ever evolving industry such as the pharmaceutical industry, we can hope that advances will always be made, technology improved, and diseases discovered and cured, but this process will also probably result in an ever changing set of legal and moral debates. With the advances in science and technology that we have witnessed over the past two decades, it is my opinion that a balance must be struck in order to properly utilize all of the tools available to improve living conditions and address health problems across the globe. Because of the highly globalized level of the modern pharmaceutical industry, this is not as simple as it would seem. The industry, from the point of view of generic drug companies and name brand firms alike, must realize that large pharmaceutical companies drive the market. They are responsible for nearly all of the research and development done in the field of medicine, on top of their cutting edge technological research and large scale production levels. Because of this, there is a need to protect their intellectual property. The 20 year patent system in place is effective in doing so, however, big pharmaceutical research companies must not be allowed to tie up their patents for additional years through loopholes in the legal system. The next realization necessary is the potential effectiveness of generics at combating health issues in the developing world, and providing inexpensive drugs across the globe. In 2001 and 2003, the WTO amended the TRIPS agreement in order to allow for some level of generics to be made available to countries that were deemed in the middle of a health crisis. This allowed certain patents to be bypassed, and proved to do two things: First, provide necessary aid to ailing African nations, and leave the necessary funding for research in tact for the leading pharmaceutical companies. It is compromises such as this that will provide the necessary balance in the coming years without undermining the companies that drive the industry.

On top of the generics debate, the FDA and organizations similar to them can make improvements to better the health conditions of the world. These improvements would be beneficial regardless of whether a drug is a generic or name brand. By streamlining their testing and approval processes, they could enable drugs to become available quicker regardless of price. Because they would be more readily available, and the companies could lower prices and receive revenue quicker while still maintaining their development and production budgets. Finally, generic drugs can be available in specific clinics in developed nations as well. While wealthier hospitals would still fall under the existing laws and guidelines regarding generics, necessary drugs could be available at clinics to those who need them the most yet cannot gain the access they need.

Both generics and name brand drugs have their strong points. The true test for the industry in coming years will be striking a balance that allows each side to improve the other. With patents protected, name brand companies will drive research and development while generics will work to make inexpensive versions widely available globally. With the success the generic companies achieve, the name brand companies will be continually motivated to improve in order to repeat the cycle, and the compromise will ever evolve

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